

REMARKS

Claims 1-27 are pending. Non-elected claims 28-31 have been canceled as a result of the restriction requirement.

The amendments to the claims are supported by the specification at page 6, lines 8-12, page 8, lines 31-34, page 12, lines 10-11, page 13, lines 13, 14 and 16-18 and Examples 4 and 5.

Specifically, the replacement of “preparing” with “fermenting” in step a) of claim 1 is supported by the specification at page 2, lines 26-31 and page 3, line 2. Page 3, lines 16-20, of the specification and Examples 4 and 5 (page 12, line 13 and page 13, line 4).

In particular, the insertion of “an assimilable carbon source and an assimilable nitrogen source” in claim 1 is supported by page 3, lines 19-20, of the specification.

Furthermore, the insertion of “in the fermentation broth to improve the yield of the 6'-O-carbamoyl tobramycin” in step b) of claim 1 is supported by the specification at page 3, lines 16-20, and page 8, lines 3-5, which disclose regulating constant levels of assimilable carbon source and assimilable nitrogen source in a fermentation process for controlling the production of 6'-O-carbamoyl tobramycin, and Examples 4-5 versus Examples 1-3 demonstrated that controlling constant levels of the assimilable carbon source and assimilable nitrogen source resulted in higher yields of 6-O-carbamoyl tobramycin.

Also, the amendment to claim 7 is supported by the specification at page 6, line 27.

Applicants submit that the amendments to step a) of claim 1 would not narrow the scope of the amended recitations because, reading steps a) and b) of claim 1 as originally filed together, a person skilled in the art would have understood that the fermentation broth also contains the

assimilable carbon source and assimilable nitrogen source, and that the 6'-O-carbamoyl tobramycin recovered in step c) of claim 1 as original filed is produced with fermentation of the fermentation broth. The amendments to step b) of "regulating a constant ~~level~~ levels of the assimilable carbon source and assimilable nitrogen source in the fermentation broth" would not narrow the scope of the amended recitations because the amendments are either cosmetic (to improve the recitations grammatically) or the inserted phrase of "in the fermentation broth" was inherent in step b) of claim 1 as originally filed. The insertion of "to improve the yield of the 6'-O-carbamoyl tobramycin" in step b) of claim 1 also would not narrow the scope of the amended claim recitation because the insertion is a recitation of the results of regulating the constant levels of the assimilable carbon source and assimilable nitrogen source.

The amendments to claims 4-6, 9, 10, 14, 15 and 20 are cosmetic, made in order to provide proper antecedent bases and would not narrow the scope of the amended claim recitations. The amendments to claims 16-18 and 24-27 are purely grammatical and would not narrow the scope of the amended claim recitations.

The Advisory Action asserts that there was broadening of "glucose" to "carbon source" in claims 4-6, and the broadening of "ammonia nitrogen" to "nitrogen source" in claims 14-15. Applicants respectfully disagree because claims 4-6 depend on claim 3 which recites "the assimilable carbon source is glucose" and claims 14-15 depend on claim 11 which recites "the assimilable nitrogen source is ammonia nitrogen." Thus, the replacement of "glucose" with "assimilable carbon source" in claims 4-6, and the replacement of "ammonia nitrogen" with "assimilable nitrogen source" in claims 14-15 are not broadening. Rather the replacements have

been done to provide consistency in view of claim 1 (“assimilable carbon source” and “assimilable nitrogen source” are recited in claim 1).

Claim Rejections - 35 U.S.C. § 103(a)

Applicants respectfully traverse the obviousness rejection of claims 1-27 over Ott *et al.* (GB 2,114,978) taken with Tomita *et al.* (US 4,032,404) and Venek *et al.* (“Selection and Accumulation in Open Systems” in Overproduction of Microbial Metabolites, ed. by Z. Vanek and Z. Hostalek, 1986, pp. 191-195).

Ott *et al.* discloses a process for producing a fermentation broth containing 6'-O-carbamoyl tobramycin by incubating a nutritive medium containing a 6'-O-carbamoyl tobramycin producing strain MNG204 of *Streptomyces tenebrarius*, and organic carbon and nitrogen sources in a submerged, aerated culture at 33 to 40°C, pH 7.2 to 7.4, in a shaker until a substantial amount of 6'-O-carbamoyl tobramycin is accumulated; and then the 6'-O-carbamoyl tobramycin is isolated (page 2, lines 27-38; page 3, lines 4, 5 and 14; page 4, line 15).

Tomita *et al.* discloses a fermentation process for producing 6'-O-carbamoyl tobramycin by culturing a strain of 6'-O-carbamoyl tobramycin producing *Streptoalloteichus hindustanus* in an aqueous nutrient medium containing assimilable sources of carbon and nitrogen in a submerged aerobic culture in sterile tanks (column 10, line 64 to column 11, line 5 and column 11, lines 32-37).

Ott *et al.* and Tomita *et al.* differ from claims 1-27 at least in not teaching or suggesting regulating constant levels of the assimilable carbon source and assimilable nitrogen source in the

fermentation medium. The Office Action attempts to rely on Vanek *et al.* to cure this deficiency but fails as explained below.

The Office Action relies on Vanek *et al.* for the teaching that chemostats were known in the prior art. On the account that chemostats were known, the Office Action concludes that claims 1-27 would have been obvious over Ott *et al.* taken with Tomita *et al.* and Vanek *et al.* In other words, merely because chemostats were known, the Office Action takes a position that it would have been obvious to regulate constant levels of the assimilable carbon source and assimilable nitrogen source in the fermentation process of Ott *et al.* or Tomita *et al.* Applicants respectfully disagree.

The fact that chemostats were known in the prior art only shows that regulating constant levels of the assimilable carbon source and assimilable nitrogen source in the fermentation media of Ott *et al.* and Tomita *et al.* **can be done**. But the mere showing that what is in the prior art is **capable of** being modified to arrive at the claimed invention is not sufficient to support *prima facie* obviousness unless there is a suggestion or motivation for the modification. *See In re Fritch*, 23 USPQ2d 1780 (Fed. Cir. 1992). In the present case, there was no motivation to modify the process of Ott *et al.* or Tomita *et al.* by using a chemostat of Vanek *et al.* to regulate constant levels of the assimilable carbon source and assimilable nitrogen source in the fermentation medium. Neither Ott *et al.* nor Tomita *et al.* suggests regulating constant levels of the assimilable carbon source and assimilable nitrogen source in the fermentation medium, or points out any benefit of regulating constant levels of the assimilable carbon source and assimilable nitrogen source. Vanek *et al.* also does not suggest regulating constant levels of the

assimilable carbon source and assimilable nitrogen source in the fermentation medium.

Applicants note that Vanek *et al.* merely teaches using chemostats to select and enrich certain mutants of the microorganism growing in a fermentation medium (please see the section title, “IV. Selection and Accumulation in Open Systems” in page 191; page 191, the last two paragraphs; page 192, the 2nd to 4th full paragraphs; page 195, the first 3 paragraphs). Thus, there was no suggestion or motivation to modify the process of Ott *et al.* or Tomita *et al.* by using a chemostat of Vanek *et al.* to regulate constant levels of the assimilable carbon and nitrogen sources in the fermentation medium used in the process of Ott *et al.* or Tomita *et al.* As a result, claims 1-27 would not have been *prima facie* obvious over Ott *et al.* taken together with Tomita *et al.* and Vanek *et al.*

Another reason why claims 1-27 would not have been *prima facie* obvious over Ott *et al.* taken together with Tomita *et al.* and Vanek *et al.* is that the prior art does not teach that modifying the process of Ott *et al.* or Tomita *et al.* by using the chemostat of Vanek *et al.* to regulate constant levels of the assimilable carbon and nitrogen sources in the fermentation medium would result in an improved yield of the 6'-O-carbamoyl tobramycin as required by step b) of claim 1. Ott *et al.*, Tomita *et al.* and Vanek *et al.* are silent on improving the yield of the 6'-O-carbamoyl tobramycin in the process of Ott *et al.* or Tomita *et al.* There was no reasonable expectation of success (improved yield of the 6'-O-carbamoyl tobramycin) if one of ordinary skill in the art were to modify the process of Ott *et al.* or Tomita *et al.* by using the chemostat of Vanek *et al.* to regulate constant levels of the assimilable carbon and nitrogen sources in the fermentation medium. However, any *prima facie* obviousness requires that the modification of

the prior art as alleged by a patent examiner to arrive at the claimed invention has a reasonable expectation of success. See *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 18 USPQ2d 1016 (Fed. Cir. 1991); MPEP 2143.02.

Since the Office Action fails to show that claims 1-27 would have been *prima facie* obvious over the prior art references relied upon, claims 1-27 should not have been rejected as obvious.

A further reason why claims 1-27 would not have been obvious over Ott taken together with Tomita and Vanek is that the improved yields of the 6'-O-carbamoyl tobramycin achieved by regulating constant levels of the assimilable carbon and nitrogen sources (please see Examples 4 and 5 in comparison with Examples 1-3) discovered by the present inventors were unexpected results. The prior art does not teach or suggest that regulating constant levels of the assimilable carbon and nitrogen sources in a fermentation medium containing a 6'-O-carbamoyl tobramycin producing microorganism would result in improved yields of the 6'-O-carbamoyl tobramycin. Withdrawal of the obviousness rejection is requested.

Responses to Examiner's Obviousness Comments in the Advisory Action

The Advisory Action is partially correct in asserting that applicants argued that there was no motivation to combine the teachings of Ott *et al.* and Tomita *et al.* with the teachings of Vanek *et al.* However, the Advisory Action alleges a wrong reason. The Advisory Action asserts that the applicants argued on the lack of motivation to combine the teachings "because Vanek *et al.* does not produce tobramycin." Actually, applicants has based the lack-of-

motivation-to-combine-the-teachings argument not only on that fact that Vanek *et al.* does not produce tobramycin. To be more accurate, one of the bases of the applicants's argument of the lack of motivation to combine the teachings is that the prior art references relied upon by the Office Action do not provide any suggestion or motivation of using the teachings of Vanek *et al.* to modify the teachings of Ott *et al.* and Tomita *et al.* Ott *et al.* and Tomita *et al.* do not teach or suggest the desirability of regulating constant levels of assimilable carbon source and assimilable nitrogen source in the fermentation processes of producing 6'-O-carbamoyl tobramycin. Of course, Vanek *et al.* also does not teach or suggest the desirability of regulating constant levels of assimilable carbon source and assimilable nitrogen source in the fermentation processes of producing 6'-O-carbamoyl tobramycin because Vanek *et al.* is totally silent on the production of 6'-O-carbamoy tobramycin. As discussed above, Vanek *et al.* merely discloses the use of chemostats to select and enrich certain mutants of the microorganism growing in a fermentation medium (page 191, the last two paragraphs, discloses that the desired mutant having a higher growth rate under given conditions will, in a continuously growing culture maintained with a chemostat, preferentially utilize the limiting nutrient and grow, while wild type cells growing at a lower rate will disappear because of the continuous dilution of the culture). A person of ordinary skill in the art would not have been motivated to use the teachings of Vanek *et al.* concerning the selection and enrichment of mutants to modify the process of Ott *et al.* or Tomita *et al.* aimed at producing 6'-O-carbamoyl tobramycin. Without a motivation to modify the process of Ott *et al.* or Tomita *et al.* with the teachings of Vanek *et al.*, claims 1-27 would not have been obvious over Ott *et al.* take with Tomita *et al.* and Vanek *et al.*

The Advisory Action states that “there is no indication of record that yield of 6’-O-carbamoyl tobramycin may be improved merely by using constant levels of any carbon and nitrogen source.” Applicants respectfully disagree. Pages 3, lines 16-20 and page 8, lines 3-5 of the specification disclose that regulating constant levels of any assimilable carbon and nitrogen source would result in improved yield of 6’-O-carbamoyl tobramycin, as exemplified by Examples 4 and 5, versus Examples 1-3.

The Advisory Action states that it is “well recognized that antibiotic production is influenced by the nitrogen, carbon and phosphate sources used in the medium.” However, applicants want to emphasize that knowing that the production of some antibiotics is influenced by the nitrogen, carbon and phosphate sources used in the fermentation medium **does not necessarily mean that** a person of ordinary skill in the art would have known or reasonably predicted that regulating constant levels of assimilable carbon source and assimilable nitrogen source in the fermentation medium would result in improved yield of 6’-O-carbamoyl tobramycin.

The Advisory Action states that “applicant has failed to demonstrate that “constant level” is all that is required to achieve” improved yields of 6’-O-carbamoyl tobramycin. Applicants respectfully disagree. As discussed above, the specification already discloses that regulating constant levels of any assimilable carbon and nitrogen source would result in improved yield of 6’-O-carbamoyl tobramycin. The Examiner has not put forth any evidence or valid scientific reason why she doubted the disclosure in the specification. Even though Examples 4 and 5 show only some of the embodiments of the invention, applicants are not required to exemplify every

embodiment of the invention.

Conclusion

In light of the above reasoning, applicants submits that the application is in a condition for allowance. A Notice of Allowance is believed in order. If the Examiner deems that there are issues that can be resolved by a telephone interview, the Examiner is urged to telephone the undersigned at.

In the event that this paper is deemed not timely, applicants petition for an appropriate extension of time. The petition fee and any other fees that may be required in relation to this paper can be charged to Deposit Account No. 11-0600, referencing the Attorney Docket No. 02664/47002.

Respectfully Submitted,

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